REMARKS/ARGUMENTS

Withdrawl of Finality

The Detailed Action indicates the application is eligible for continued examination under 37 CFR 1.114, and because the fee set forth in 37 CFR 1.17(e) was timely paid in conjunction with a Request for Continued Examination (RCE), the finality of the previous Office Action has been withdrawn. The Action further indicates that the submission filed in support of the RCE and the Supplemental Response filed on February 7, 2005 were both entered and that the new claims (claims 9-16) filed with the RCE will be examined.

Amendment(s) to the Specification

The Office Action states that the application fails to comply with the sequence rules, set forth in 37 CFR 1,821-1.825. This is based on the observation that Figures 6 and 9 contains sequence which have not been identified by SEQ ID NO:. In an attempt to bring the application into compliance with the sequence rules, Applicants have amended the text of the brief descriptions of Figures 6 and 9 by including a parenthetical cross reference to the SEQ ID NO.: of the sequences that are displayed in the figures.

No new matter has been added by virtue of these amendments.

If the Examiner finds that these amendments are insufficient to bring the application into compliance with the sequence rules, Applicants will submit replacement figures for Figures 6 and 9 upon the determination that there is allowable subject matter in the application.

Status of Claims

Claims 1-4 and 8-16 are pending in the application. The claims under examination are drawn to two alternatively spliced forms of the human motilin receptor (MTL-R1A and MTL-R1B) which is a G protein coupled receptor.

Claims 5 and 6 have been previously canceled. Claim 7 has been previously withdrawn from consideration. Claims 2, 3, and 9 are canceled by the instant amendment. After entry of this amendment, Claims 1, 4, 8, and 10-16 will be under examination.

Subject Matter of the Invention Under Examination

The instant specification discloses two alternatively spliced forms of the human motilin receptor, referred to as MTL-R1A and MTL-R1B. SEQ ID NOS 1-5 provide genomic DNA sequence for the human motilin gene and nucleic acid acid and amino acid sequences for MTL-R1A and MTL-R1B receptors.

More specifically:

SEQ ID NO: 1 discloses a genomic human motilin gene DNA sequence including 5' untranslated sequence and intronic sequences (page 3, lines 15-17);

SEQ ID NO: 2 discloses the cDNA sequence for MTL-R1A;

SEQ ID NO: 3 discloses the deduced amino acid sequence encoded by SEQ ID NO: 2;

SEQ ID NO: 4 discloses the cDNA sequence for MTL-R1B;

SEQ ID NO: 5 discloses the deduced amino acid sequence encoded by SEQ ID NO: 4.

The invention disclosed and claimed in the instant application is based on the discovery that MTL-1RA is the endogenous receptor for motilin. This finding removed CD38 from the list of orphan GPCR receptors known to the art at the time of applicant's invention.

Applicants respectfully request reconsideration of the application in view of the foregoing amendments of the claims and specification and the following remarks and reasoning.

Claim Amendment(s)

Please cancel claims 2, 3, and 9. In order to advance prosecution of this case on the merits Claims 1, 4, 8, and 10, 11, 12, 14, 15 and 16 have been amended to overcome the outstanding rejections raised in the Office Action mailed April 19, 2005.

More specifically, Claim 1 has been amended to recite:

1. An isolated polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 3 which functions as a receptor for motilin.

Support for the structural and functioal limitations of amended claim 1can be found in Example 1 on page12, lines 9-15 and lines 20- 25, wherein Applicants present data demonstrating that MTL-R1A is the receptor for motilin.

Claim 4 has been amended to recite:

4. An isolated polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence set forth in SEQ ID NO:2 which functions as a receptor for motilin.

The support cited above for the subject matter of amended claim 1 also provides support for amended claim 2.

Claim 8 has been amended to recite:

8. A method for determining whether a test compound is capable of agonizing or antagonizing motilin binding comprising:

(a) transfecting indicator cells with an expression vector consisting of the nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:2;

(b) exposing the indicator cells to the test compound in the presence of detectably labeled motilin;

(c) measuring the amount of motilin binding to the indicator cells;

(d) comparing the amount of motilin binding to the indicator cells with the amount of motilin binding to cells exposed to the detectably-labeled motilin in the absence of a test compound wherein if the amount of motilin binding to the indicator cells in the presence of the test compound differs from the amount of motilin binding in the absence of the test compound, then the test compound is capable of agonizing or antagonizing motilin binding.

Support for the subject matter of the amended claim can be found particularly on page 8, line 27 to page 9, line 2, wherein Applicants indicate that the expression of the cloned MTL-R1A receptor provides an effective method for the rapid selection of compounds with high affinity for a motilin receptor. Applicants further indicate that compounds identified in a MTL-R1A-based screening assay are likely to be agonists or antagonists of motilin binding.

Claim 10 has been amended to recite:

10. An isolated nucleic acid comprising a nucleotide sequence encoding a polypeptide which functions as a human motilin receptor, wherein the nucleic acid sequence is selected from the group consisting of:

(a) a nucleic acid sequence consisting of the nucleotide sequence of SEQ ID NO:2;
(b) a nucleic acid sequence consisting of a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence of SEQ ID NO: 3 ;
(c) a nucleic acid sequence consisting of the nucleotide sequence of SEQ ID NO: 1; and
(d) a cDNA sequence isolated from a host cell transfected with the nucleic acid of SEQ ID NO: 1 which encodes a polypeptide that functions as a receptor for motilin.

Support for the subject matter of the amended claim can be found in Examples 2, 3 and 4 of the specification. More specifically, support for the recitation of element (a) can be found in example 3, on page 13 lines 4-5, and example 4, wherein Applicants describe the preparation and use of cells transfected with MTL-R1A plasmid DNA. Support for element (c) is found in example 1, on page 11, lines 7-10, wherein Applicants describe the use of cells transfected with the MTL-1 genomic construct which comprises the nucleotide sequence set forth in SEQ ID NO:1. Support for element (b) can be found in example 2 wherein applicants describe the use of cells expressing MTL-R1A. Element (d) is supported by the cells described and exemplified in Example 1, wherein HEK-293/aeq 17 cells were transfected with the MTL-1 genomic construct (which comprises SEQ ID NO:1) and used as a source of nucleic acid (cDNA) to construct a MTL-1A plasmid which was used to transfect cells. The resulting cells are demonstrated to express full-length MTL-R1A.

Claim 11 has been amended to recite:

11. An isolated nucleic acid molecule encoding a protein according to claim ~~3~~ 1, wherein the nucleic acid consists of a cDNA sequence isolated from a human thyroid DNA library.

Support for the subject matter of the amended claim can be in Example 1 on page 11, lines 7-15 wherein Applicants describe the experiment which confirmed the existence of two motilin receptor mRNA splice variants. Applicants specifically describe using the MTL-1 genomic construct isolate by RACE reactions from human thyroid DNA to transfect HEK-293/aeq 17 cells. Characterization of the resulting poly (A)+ mRNA from the transfectrants confirmed the existence of two splice variants and directly lead to the isolation of MTL-R1A cDNA.

Claim 12 has been amended to recite:

12. An isolated cDNA encoding a polypeptide that functions as a human motilin receptor wherein the cDNA consists of a nucleic acid isolated from a host cell transfected with an expression vector comprising SEQ ID NO:1.

The portion of the specification identified above as support for amended claim 11, also provides support for the subject matter of amended claim 12.

Claim 14 has been amended to recite:

14. An expression vector comprising a nucleic acid comprising a nucleotide sequence that encodes a polypeptide which functions as a human motilin receptor, wherein the nucleic acid sequence is selected from the group consisting of:

(a) SEQ ID NO:1;
(b) SEQ ID NO:2;
(c) a nucleotide sequence encoding the amino acid sequence set forth in SEQ ID NO: 3: and
(d) a cDNA sequence isolated from a host cell transfected with the nucleic acid of SEQ ID NO: 1 which encodes a polypeptide that functions as a receptor for motilin.

Support for the recitation of a nucleic acid sequence comprising a nucleotide sequence that encodes a polyeptide which functions as a human motilin receptor can be found throughout the specification. In particular support can be found in the cells exemplified in examples 2, 3 and 4.

Claims 15 and 16 have been amended to recite:

15. A recombinant host cell transfected with a vector according to claim 14.

16. A recombinant host cell expressing a human motilin receptor, wherein said motilin receptor consists of an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

Support for the recitation of a "recombinant host cell" in claims 15 and 16, can be found in the cells exemplified in examples 2, 3 and 4 of the specification, wherein HEK-293 cells were transfected with MTL-R1A cDNA.

No new matter has been added by way of the above-described claim amendments.

The Rejection of Amended Claims 1, 3 and 4 Under 35 U.S.C. §102 Should be Withdrawn

The rejection of amended claims 1, 3 and 4 under 35 U.S.C. §102 were maintained. The rejection of claim 2 as amended was withdrawn. The Office Action indicates that Applicant's arguments based on the teachings of Figure 1 of the McKee *et al.* Genomics publication (Genomics 46: 426-434 (1997)) were fully considered and found persuasive in part. The Action further indicates that although the polypeptide taught in Figure 1 of the McKee *et al.* is longer than the polypeptide disclosed in SEQ ID NO: 3 (which is encoded by SEQ ID NO:2) the fact that claims 1, 3, and 4 recited comprising language the claims read on the prior art sequences.

The cancellation of claim 3 partially obviates this rejection. The rejection is completely obviated by the fact that the claims 1 and 4 have been amended to replace the term "comprising" with the term "consisting of." The recitation of closed language in the amended claims prevents the amended claims from reading on the teachings of the prior art.

More specifically, amended claim 1 recites "an isolated polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:3." As disclosed in the specification, SEQ ID NO:3 is a 412 amino acid protein. Accordingly, as amended claim 1 does not read on the 438 amino acid protein provided in Figure 1 of the McKee *et al.* Genomics publication.

As amended claim 4, in relevant part, recites "an isolated polypeptide consisting of the amino acid sequence encoded by the nucleotide sequence set forth in SEQ ID NO:2 which functions as a motilin receptor."

As disclosed in the specification, SEQ ID NO:2 provides a nucleotide sequence which consists of 1239 base pairs which represents the coding sequence for the 412 amino acid MTL-R1A polypeptide presented in SEQ ID NO:3. As amended claim 4 is free of the teachings of Figure 1 of the McKee *et al.* publication, because 1) Figure 1does not include any nucleotide sequence information; 2) the coding sequence provided in SEQ ID NO:2 of the specification is not long enough to encode the 438 amino acid protein presented in Figure 1; and 3) the McKee *et al.* publication does not teach or suggest that SEQ ID NO:2 encodes an endogenous receptor for motilin.

Accordingly, the rejection of Claims 1 and 4 based on the teachings of Figure 1 of the McKee *et al.* publication have been obviated. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection of Claim 8 Under 35 U.S.C. §103 Should be Withdrawn

The Rejection of Claim 8 under 35 U.S.C. §103 was maintained. The Examiner summarized Applicants' argument of record as being primarily grounded in the fact that "because McKee *et al.* (1) did not disclose the nucleotide sequence of the genomic clone, and (2) provided incorrect amino acid sequence information for GPR38, it is unlikely that an artisan would have succeeded at producing host cells expressing functional GPR38 receptors" (Office Action, page 4).

When the argument of record was advanced, undersigned was not aware of the NCBI submissions (AF034633 and AF034632) that were deposited in support of the McKee *et al.* Genomics publication. Accordingly, the prior argument was concerned with overcoming rejections based on the teachings contained within the four corners of the publication itself. More specifically, the arguments of record focused on distinguishing the amino acid sequence information provided in Figure 1 of McKee *et al.* publication from the sequence information disclosed and claimed in the instant application.

Maintenance of the rejection is grounded in the Examiner's position that the "teachings of Weinshank *et al.'s* disclosure relating to a method for determining whether a ligand is capable of binding to a specific GPCR, or contemporaneous knowledge at the time of Applicant's

invention provides the requisite sequence information required to produce a host cell expressing a functional human GPR38 receptor" (*Id.*). It should be noted that the Examiner's position was based on a consideration of the combined teachings of the information contained within the four corners of the Genomic publication AND the NCBI sequence submissions.

Based on the combined teachings of McKee *et al*'s Genomic Publication and the sequence information provide by AF034632 skilled artisans at the time of Applicants' invention had access to: 1) the genomic nucleotide sequence of MTL-1, and 2) instructions for producing a mRNA that encodes MTL-1RA splice variant. Assuming arguendo, that a skilled artisan produced a host cell expressing CD38, the artisan would have merely have succeeded at producing with a host cell which expressed an orphan GPCR receptor.

Claim 8 has been amended to recite:

> 8. A method for determining whether a test compound is capable of agonizing or antagonizing motilin binding comprising:
>
> (a) transfecting indicator cells with an expression vector consisting of the nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:2;
>
> (b) exposing the indicator cells to the test compound in the presence of detectably labeled motilin;
>
> (c) measuring the amount of motilin binding to the indicator cells;
>
> (d) comparing the amount of motilin binding to the indicator cells with the amount of motilin binding to cells exposed to the detectably-labeled motilin in the absence of a test compound wherein if the amount of motilin binding to the indicator cells in the presence of the test compound differs from the amount of motilin binding in the absence of the test compound, then the test comound is capable of agonizing or antagonizing motilin binding.

Because it was NOT know that the MTL-R1A receptor is the endogenous receptor for Motilin prior to this disclosure, an investigator would not have been able to use the prior art teachings of McKee *et al.* and Weinshank *et al.* to identify agonists or antagonists of motilin binding. More specifically, skilled artisans would not have used the available information to design an assay comprising all of the steps of amended claim 8, or to perform determine whether test compounds agonized or antagonized motilin binding.

In view of the above-described amendments to claim 8 the outstanding obviousness rejection has been overcome. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection of Claim 16 Under 35 U.S.C. §101 Should be Withdrawn

Claim 16 is rejected under 35 U.S.C. §101 because the claimed invention was directed to non-statutory subject matter. As originally drafted claim 16 was directed to a host cell expressing a human motilin receptor. Therefore, the scope of the original claim encompassed naturally occurring cells that express the motilin receptor.

Claim 16 has been amended to recite "A recombinant host cell expressing a human motilin receptor, wherein said motilin receptor consists of an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5."

Accordingly, the amended claim reflect the hand of man and the rejection has been obviated. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection of Claims 10 and 14 Under 35 U.S.C. §112, Second Paragraph, Should be Withdrawn

Claims 10 and 14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claimed the subject matter which applicants regard as the invention. More specifically, the claims are alleged to be indefininte because the term "motilin receptor" does not provide any structural limitations, with the effect that the metes and bounds of the claim allegedly cannot be determined..

Applicants traverse this indefiniteness rejection of claim 10 on the grounds that body of the claim (i.e., the lettered alternatives a), b) and d)) expressly recite SEQ ID NOS: the nucleotide sequences of which provide the structural limitations of the claimed nucleic acid. The third alternative c) has been amended to recite " a nucleic acid sequence consisting of the nucleotide sequence of SEQ ID NO:1."

Recitation of the term "motilin receptor" in the preamble requires that the polypeptide product of the claimed nucleic acid performs a specific function, namely that it functions as a receptor for motilin. More specifically, the claim is directed to nucleic acid sequences which comprise at least one of 4 alternative embodiments all of which encode a polypeptide that functions as a receptor for motilin. In each of the 4 alternatives the structure of the claimed nucleic acid is dictated by a SEQ ID NO:.

Accordingly, Applicants are of the opinion that the amended claim distinctly particularly points out and distinctly claims the subject matter that they regard as the invention. Because the

t rejection has been obviated, Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection of Claims 10, 13, 14, and 15 Under 35 U.S.C. §112, First Paragraph, Should be Withdrawn

Claims 10, 13, 14, and 15 are rejected under 35 U.S.C. §112, first paragraph, because the specification, allegedly does not enable any person skilled in the art to use the invention commensurate in scope with the claims.

Independent claims 10 and 14 have been amended to recite nucleic acids which consist of of a nucleotide sequence selected from the sequences set forth in SEQ ID NOS: 1, 2 or 4 or a nucleotide sequence which encodes a polypeptide consisting of the amino acid sequence of SEQ ID NO: 3.

Based on the Examiners finding of record that:the specification is enabling for "a motilin recpeot polynucleotide (the polynucleotide having the nucleic acid sequence disclosed in SEQ ID NOS: 1, 2, and 4) encoding the amino acid sequence disclosed in SEQ ID NOS: 3 and 5, expression vector containing said polynucleotide and host cells" (Office Action, page 7), the subject matter of the amended claims is enabled by the disclosure. Accordingly, the rejection of claims 10 and 14 has been obviated.

The above-described amendment to claim 10, which is the base claim for dependent claim 13, obviates the enablement rejection of claim 13. Similarly, the above-described amendment to claim 14, which is the base claim for dependent claim 15, obviates the rejection as it relates to claim 15.

Applicants are of the opinion that the specification enables a person silled in the art to use the invention commensurate in scope with the amended claims. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection of Claims 10, 13, 14, and 15 Under 35 U.S.C. §112, First Paragraph, Should be Withdrawn

Claims 10, 13, 14, and 15 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification is such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention.

The written description rejection is grounded in the findings that: 1) the name "motilin receptor" does not provide and structural limitations nor does it automatically infer a functionality; and 2) the claims as written encompass polypeptides which may vary substantially in length and also in amino acid/polynucleotide composition. The Examiner goes on to state that the "disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of a specific polypeptide is insufficient to describe the genus" (Office Action, page 10).

The amendment of independent claims 10 and 14 to change each of the limitations, (a) – (e) and (a) – (d), respectively, obviates the rejection to the extent that it is grounded in an alleged lack of structural limitations.

In order to advance the prosecution of the application Claims 10 and 14 have been amended to avoid recitation of the limitation "a cDNA sequence encoding a motilin receptor isolated from a human thyroid library."

The disclosure provided in the application clearly establishes that applications were in possession of "a cDNA sequence encoding a motilin receptor isolated from a host cell transfected with the nucleic acid sequence of SEQ ID NO:1" (Office Action, page 9). Furthermore, the guidance provided on page 11, lines 7-15 provides sufficient written description to enable a skilled artisan to reduce this embodiment to practice. Accordingly, Applicants are of the opinion that the instant specification provides and adequate description of the genus of polynucleotide/polypeptides encompassed by the amended claims.

Applicants traverse the Examiner's finding that "[t]he name motilin receptor does not automatically infer a functionality" (Office Action, page 9). One of skill in the art would readily acknowledge that the term "motilin receptor," connotes a cell surface receptor which binds motilin. This position is consistent with the fact that at the time of Applicant's invention the prior art had knowledge of the structure, and biological function of motilin, as well as an expected mode of action for its receptor.

Furthermore, the results of Examples 2, 3, and 4 of the specification establish the function of the motilin receptor. Therefore, even in the absence of the prior art knowledge of motilin, and the expected mode of action of its naturally occurring receptor, Applicant's disclosure clearly establishes the functionality of the disclosed receptors. For Example, Example 2 provides radioligand binding studies using [^{125}I] human motilin and cell membranes prepared from cells transfected with MTL-R1A. The results establish that MTL-R1A expression confers

high affinity and specific binding which is G protein coupled. Example 4 provides a structure-function analysis, the results of which indicate that the motilin peptide, contains an N-terminal region (amino acids 1-7) essential for activity, and further indicate that the "rank order of potency of several motilin peptide analogs correlates with their reported potency measured by *in vitro* contractility assays performed on native motilin receptors.

Therefore, a skilled artisan reading the information provided in the instant disclosure would readily understand that the term "motilin receptor," connotes a polypeptide/receptor which binds motilin.

Accordingly, the written description rejection has been obviated. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection of Claims 1, 3, 4, 9-16 Under 35 U.S.C. §102 Should be Withdrawn

Claims 1, 3, 4, 9, 10, 11, 12, 13, 14, 15, and 16 are rejected under 35 U.S.C. §102(a) as being anticipated by McKee *et al.* The Office Action indicates that McKee et al. discloses GPR38 receptor polynucleotide/polypeptide which has 100% query match to the coding region of SEQ ID NO: 1 (which comprises SEQ ID NO:2 and encodes SEQ ID NO: 3). The Action further indicates tha the McKee *et al.* further discloses a vector containing the polynucleotide and cells containing the vector, thereby allegedly meeting the limitations of the rejected claims. In addition, it is noted that the GPR38 genomic clone referred to on page 427 column 1, second paragraph, inherently has the sequence which encodes the claimed polypeptide.

The rejection of claim 1 has been partially obviated due to the fact that it has been amended to recite:

1. An isolated polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 3 which functions as a receptor for motilin.

As amended claim 1 now recites a functional limitation which requires that the claimed polypeptide functions as a receptor for motilin. The entire teachings of McKee *et al.*, (i.e. the total information contained in the text and figures of the publication and the sequence information disclosed in the NCBI submissions) do not teach that the CD38 receptor is the endogenous receptor for motilin. Accordingly, the amended claim is free of the prior art.

The judicially created doctrine of inherency applies when an element or aspect of the invention is deemed to be part of the reference (or the prior art) because that aspect is necessarily associated with the thing described in the reference. However, case law has established that the mere possibility that a specific result or characteristic may occur, or be present, in the prior art is

not sufficient to establish inherency of that result or characteristic. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art" In re Robertson, 49 USPQ2d 1949, 1950-51 (Fed. Cir.1999).

G protein coupled receptors (GPCRs) represent a large and diverse family of receptors with diverse function and properties. GPCRs have no well-established utility based on family membership or sequence homology with other GPCRs. It is well known that receptor function cannot be reliably be predicted from DNA or amino acid sequence homology. The teachings of McKee *et al.* do not provide any guidance based on structure/function analysis or homology which would allow an artisan to be able to identify motilin as the ligand for the CD38 receptor which is disclosed in that publication.

The fact that the genomic MTL-1 sequence set forth in SEQ ID NO:1 encodes two distinct mRNAs that encode alternative splice variants, only one of which is functional indicates that the a receptor capable of functioning as a receptor for motilin is not "necessarily present" and does not "necessarily flow" from the teachings of the McKee *et al* publication. In fact, as previously argued, the actual teachings of the reference itself incorrectly identifies the open reading frame which led the authors to provide an incorrect amino acid sequence in Figure 1 of the reference.

Furthermore, there is nothing inherent the nucleotide sequence of a receptor gene that is reported as being related to the growth hormone secretagogue or neurotensin receptor which would lead one of skill in the art to know that motilin would be the ligand for MTL-R1A. The fact that although motilin receptor characterization was actively pursued in human and other species for over 25 years after the isolation of motilin with no reports of successful cloning also attests to the novelty of Applicant's invention. This is further substantiated by Applicants' statement on page 5, lines 22 – 24, that even after the McKee *et al.* publication CD38 remained an orphan receptor because "efforts to isolate cDNA clones by standard library screening proved unsuccessful" lends further support to the noninherent nature of Applicants' invention, and to the fact that based on the teachings of McKee *et al.* one of ordinarly skill in the art would NOT have recognized that CD38 is the endogenous receptor for motilin.

Based on the disclosure provided in the specification Applicants were the first investigators to determine that the MTL-R1A receptor (CD38) is the endogenous receptor for motilin. By elucidating the ligand for CD38 the inventors have conferred the CD38 sequence with a utility which in light of their discovery allows investigators to use the sequences to produce vectors and host cells which can be used to identify agonists and antagonists of motlin receptor binding.

Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection of Claim 8 Under 35 U.S.C. §103(a) Should be Withdrawn

Claim 8 is rejected under 35 U.S.C. §103(a) as being unpatentable over McKee *et al.*, in view of Weinshank *et al.* The Office Action indicates that McKee *et al.* discloses GPR38 receptor polynucleotide/polypeptide which has 100% query match to the coding region of SEQ ID NO: 1 (which comprises SEQ ID NO: 2 and encodes SEQ ID NO: 3). The Office Action further notes that McKee *et al.* state that "[f]urther studies are required to indentify the lignad-binding and functional properties of GPR38" (Office Action, page 15). Weinshank *et al.* discloses "a method for determining whether a ligand is capable of binding to a specific GPCR" (Id). The Examiner concludes that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to use the GPR38 disclosed by McKee, in the methods disclosed by Weinshank to determine which ligands were capable of binding to the newly cloned receptor. The Examiner further indicates that the ordinary artisan would have been motivated to use GPR38 in the method disclosed by Weinshank to determine, because the ligand-binding and functional properties of GPR-38 remained to be determined.

As amended claim 8 recites "a method for determining whether a test compound is capable of agonizing or antagonizing motilin binding." The recited method utilized detectably-labeled motilin in order to identify test compounds which agonize or antagonize motilin binding to the MTL-R1A receptor disclosed and claimed in the instant application.

As noted above McKee *et al.* does NOT teach that CD38 is the endogenous ligand for motilin. The disclosure provided in Weinshank *et al.* does not cure this deficiency. Applicants are of the opinion that the combined teachings of McKee *et al.* and Weinshank *et al.* represents nothing more than an invitation to experiment with no assurances of success. This reasoning is based on the existence of more than one splice variant of the human motilin receptor, the inability to predict a ligand for one receptor based on the level of sequence homology which a particular GPCR shares with another GPCR, and the vast number of potential GPCR receptor ligands that were known to the art at the time of Applicants' invention.

Accordingly, the combined teachings of the cited references do not render the subject matter of amended claim 8 obvious.

Applicants respectfully request reconsideration and withdrawal of this rejection.

Reconsideration and withdrawal of the rejection are respectfully requested.

Respectfully submitted,

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